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This final technical report covering the work accomplished on the project "Perceptual Factors in Workload: A Neuromagnetic Study", includes ddescriptions of substantive experimental studies of neural phenomena related to attention and auditory perception. It also describes efforts to enhance the superconducting instruments and other devices needed for the rapid and accurate accumulation of neuromagnetic data, and advances made in techniques for calibrating these instruments and for analyzing neuromagnetic data. The substantive experiments included a major study of the magnetic N100 phenomena and its sources and how they are affected by selective attention. Its relationship to the electrical N100 is considered, and required future research described. Also, work on the magnetic P300 phenomenon is described. This work confirmed earlier studies showing that the equivalent current dipole source is located in or near the hippocampal formation. The localization of multiple auditory sources based on work at NYU and in collaboration with the Los Alamos group is described as well. Improvements in instru-

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mentation include the installation of a new gantry for purposes of evaluation, the design of a novel device for quantifying positions in MR images, and the development of a graphics program for depicting a current dipole in the heads of subjects are also described. New methods for calibaring multisensor systems were developed, and the details are provided in the report. Finally, an opportunity arose during the course of this project to located a very small metalic object accidentally embedded in the back of a human patient. This allowed us to obtain surgical verification of magnetic methods for locating sources. The predicted postion was accurate within two millimeters. to field 18

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Final Technical Report

Background

AFOSR-TR- 88-0861

5-K-This report describes the work accomplished on our AFOSR contract No. F49620-87-0004 during the period 01/01/85 through 12/31/87. The first two years of this project were described in the preceding interim scientific reports, so this report will emphasize the work of the final year.

The goals of this project were to enhance the instrumentation and technology involved in measuring and analyzing the brain's magnetic field so that it would become possible to study the pattern of brain activity involved in various aspects of human performance. A special emphasis was placed on the way in which workload affects the activity of the brain and, ipso facto, the performance of the human operator. An equally important goal was the design and conduct of meaningful substantive experiments concerning aspects of brain activity underlying processes such as attention and its deployment in various tasks. The Following section review our accomplishments in all of these areas over the term of the project.

Early Experimental Studies

During the previous reporting periods of this project we completed a major study of selective auditory attention which was fully described in previous reports. The first publications derived from this work appeared during the current period, and a major paper based on it is being readied for submission for publication (Curtis, 1987; Curtis, et al., 1988). In this study we employed a dichotic listening paradigm in which subjects attended to strings of tone bursts presented to one ear while ignoring similar bursts of different (more than an octave away in pitch) that were presented to the other ear. The significance of this paradigm for theories of attention is traced by Treisman (1964; 1967; 1969) with a typical opposing view presented by Deutsch and Deutsch (1963). (Also see Broadbent, 1957; 1958; and Cherry, 1953.) Responses evoked by both the ignored and attended signals contain components corresponding to the N100 component of the auditory event related potential (ERP). It was found that the N100m (the magnetic counterpart to the N100 of the ERP) varied in amplitude with attention, i.e., its amplitude was greater if attention was being paid to the stimulus. A similar effect was studied in detail by Hillyard and his colleagues with electrical recordings (Hillyard, et al., 1973; 1983; 1984; 1985). The latter papers dealt largely with the effect of attention on the amplitude of the N100 component of the ERP. We went further than this in that we dealt with the problem of locating the source of the observed N100m, and computed the strength of the equivalent current dipole source. Thus, it was found that the equivalent current dipole source of the observed field of N100m was located in or near auditory cortex in the lateral sulcus. This demonstrated that activity of auditory cortex is modulated by attention. This conclusion should be contrasted with the previously widespread and prevailing view that the effect of selective attention on N100 could well be due to the summation of endogenous activity of sources distant from auditory cortex with that of exogenous activity of a source or sources in auditory cortex (see Naatanen and Picton, 1987 for a review).In view of the fact that 30 - 50% changes in source strength (current dipole moment) was attributable to attention, and that the changes in ERP amplitudes are not larger than this, we must conclude that the modulation of auditory cortical activity plays

a major role in the effect of attention on N100 of the ERP. Essentially the same results were found for conditions in which the subject's attention was allocated to stimuli that different in apparent direction (lateralization) or when the stimuli were presented to one ear and attention was allocated on the basis of a difference in pitch. No significant hemispheric conditions were observed. Despite this, there remains the possibility that other non-auditory cortex sources may contribute to the effect of attention on N100.

Although our data support a strong contribution of sources in auditory cortex to attention-related variations in N100, this does not rule out possible roles for other sources. In a spherical model radial current dipole sources make no contribution to the external magnetic field. Therefore, sources that are oriented radially with respect to the local contours of the overlying skull may be expected to make little contribution to the neuromagnetic field associated with N100m. However, these same "quasi-radial" sources would contribute strongly to the electrical N100.

One of the stronger bits of evidence that such magnetically weak or silent sources may actually be present is that by Hari, et al. (1982). These investigators found that the amplitude of the electrical N100 increased monotonically with ISI up to ISIs as great as 16 seconds. This effect is quite striking, and it is reminiscent of the psychological refractory period studied by Karlin and Kestenbaum (1968). However, the amplitude of N100m increased with ISIs only up to 8 seconds. It was concluded that additional and magnetically silent sources contributed to N100, and these were responsible for the increase in amplitude with ISI longer than 8 seconds. These sources were presumed to be radial in orientation, and not necessarily located in auditory cortex.

In the course of our work on this project we noted that Hari, et al. measured the field associated with N100m over only one hemisphere, while the vertex electrode used to detect N100 was sentitive to activity in both hemipsheres. It was postulated that asymmetrical variations in amplitude of N100 with ISI between the hemispheres could account for the discrepancy between the electrical and magnetic recordings. This would be an interesting finding in itself, but it would essentially trivialize the notion that a magnetically silent source had contributed to N100, since the hemisphere not being observed would indeed by silent, but only accidentally and not essentially.

As a follow-up to this early observation, we explored the possibility that variation in amplitude of N100m with ISI is asymmetrical, in that the sources of this component in each hemisphere show different effects of ISI. Inasmuch as one of us (L. Kaufman) was in Norway attending a NATO conference in March of 1987, it was possible to travel to Helsinki and conduct a pilot study in collaboration with R. Hari, the senior author of the paper that first described the difference between the electrical and magnetic responses as ISI is varied. (It should be noted that no travel expenses were charged to this project.) Using the same instruments and experimental paradigm as that employed in the original study by Hari, et al., it was found that the two hemispheres do indeed show different effects of ISI. Owing to the short time available for this study, it was not possible to obtain enough data so that we could evaluate the magnitude of the asymmetry and determine if it was sufficent to account for the discrepancy between the electrical and magnetic recordings. This is now being done at the Neuromagnetism Laboratory under another grant. In any event, we did show asymmetry, and in view of the fact that electrodes at one location can be affected by distant sources (even sources in a hemisphere contralateral to that over which an electrode is place), it is questionable to conclude that the different effects of ISI reveal the presence of sources that are mangetically silent.

In another study early in the project we joined forces with E. Donchin and his colleagues from the University of Illinois in an attempt to replicate our original studies of the P300 phenomenon (Okada, et al., 1982a). The significance of P300 for cognitive processes related to workload is made clear by McCarthy and Donchin (1981) and by Isreal, et al. (1980), for example. The main reason for attempting a replication is that controversy surrounds the interpretation we gave to our original data, namely, that the hippocampal formation is the most likely source of P300. We set out to replicate the McCarthy and Donchin study using the PEARL system from the University of Illinois, together with their software, in acquiring and anlyzing the data. Owing to a high level of ambient magnetic noise at low frequencies, a very large number of trials was needed to obtain enough data for detecting P300m. Therefore, we did not completely replicate McCarthy and Donchin, but we did complete a set of visual odd-ball trials and were able to map the extracranial magnetic field associated with P300. This map confirmed our earlier study in that the equivalent current dipole source was located in or near the hippocampal formation. Since the completion of that experiment, a magnetically shielded room and improved instruments (funded by the DOD-University Research Initiative Program at NYU) were installed in the Neuromagnetism Laboratory and we are now routinely acquiring P300m data with support from another AFOSR grant. This work, which is being done in collaboration with E. Donchin, has proven to be most interesting, and could not have been done without the support provided by the project that is the subject of this report. The results obtained to date will be described in a Progress Report on the University Research Initiative Program at NYU which will soon be released to AFOSR.

Localization of Sources of Long-Latency Auditory Evoked Magnetic Fields

Neuromagnetic studies of Pelizzone et al. (1984, 1985) in our laboratory demonstrated that the neural source of the N100m transient component to a 1-kHz tone burst was laterally displaced in the subject's head by about 1 cm posterior to the region that responds to steady-state stimulation at the same frequency. This showed that individual active regions of auditory cortex may be resolved, suggesting the possibility that spatial separation of the sources of other transient components may also be established. To determine to what degree this may be attained, one of us (S.J. Williamson) collaborated with the neuromagnetic group at Los Alamos National Laboratory to carry out systematic measurements with a single-sensor SQUID system of the responses to long tone bursts. This was the first quantitative analysis to determine the positions for the equivalent current dipole sources for all four long-latency components (P50m, N100m, P200m, and the steady field). All sources were found at positions indicating they lie near or in auditory cortex, consistent with published results for N100m and P200m.

A strong effect of stimulus frequency was found for the position of the source of P50m, but remarkably there were no consistent trends to the direction of the source's shift with stimulus frequency. This finding would appear to demonstrate important individual differences for the functional map of human auditory cortex. The P200m source is generally weaker than that of N100m and in some subjects may overlap the early portion of the steady field. The position of the source of the steady field could not be distinguished from that of N100m. There was, however, a clear separation of the sources of P50m and P200m from N100m. These results have been published in a report by Arthur et al. (1987).

Improved Dewar Gantry

To determine where neural sources lie within the head it is necessary to measure accurately the position and orientation of each field sensor with respect to landmarks on the patient's scalp. Traditionally the dewar containing the sensor was placed in the desired location, and the position of its tail with respect to convenient landmarks was measured across the scalp. But this procedure has inherent inaccuracies, due principally to the irregular shape of the head. One advance was to align the patient's head within a reference framework, and to move the dewar accurately with respect to this framework. The "Scanner" deviced developed in our laboratory (Williamson et al. 1984) is an example of such a setup where the dewar is held in a carriage that moves so that the dewar's axis always points toward the center of the patient's head. This has an advantage when the head is modeled as a sphere for computing source locations, for the field component provided by the sensors is exactly the radial component. Another procedure is to use a computer-controlled mechanized gantry that moves the dewar to a pre-determined position and orientation in space (Vrba et al. 1984). Recently we installed a commercial device for purposes of evaluation. Provided that the device performs properly, we shall make an effort to obtain funds to purchase it, so that it may remain in our laboratory.

The new gantry is based on a different principle which permits the operator to move the dewar by hand to the desired location. Independent movement is provided along two orthogonal horizontal directions and the vertical direction, with rotation allowed about the vertical axis and the horizontal axis where the gantry supports the dewar. Friction holds the dewar in place when the operator releases it, and a secure lock is provided by compressed gas brakes that secure all these degrees of freedom. The dewar can also be rotated about its own axis to set orientation of the individual sensors at a desired angle. The exact position and orientation of the dewar relative to the subject's head is indicated by a system known as the "Probe Position Indicator", purchased with funds from a DOD-University Research Initiative awarded by AFOSR.

"Rainbow" - A Device for Quantifying Positions in a Magnetic Resonance Image

The positions of field measurements about a subject's head are indicated in a coordinate system that we call the "head-based coordinates." It is defined with respect to the periauricular points and nasion, which are the reference positions on which the EEG 10-20 electrode system is also based. One ultimate goal of the neuromagnetism program in our laboratory is to establish a three-dimensional functional image of the brain, in which regions of neural activity are shown in relationship to anatomical features. As a first step in this direction, we developed a system to define the same head-based coordinate system for magnetic resonance images (MRIs). A plexiglass framework called "Rainbow" was devised to embraces the subject's head when the MRI is recorded. Features on Rainbow are rendered as a series of bright spots on the MRI, so that by use of a 3D digitizer (such as the Probe Position Indicator) any position on the MRI can be related quantitatively to the head-based coordinate system.

Thus by digitizing one MRI slice after another, a 3D rendition of the subject's head can - in principle - be developed. In the future such a display could be shown on a solids rendering system such as the Hewlett Packard Model 9000/350SRX workstation. For the moment, graphics facilities in our laboratory permit any 2D slice to be illustrated in line

drawing format.

One application of 3D images will be to compare the orientation of the equivalent current dipole model representing neural activity with the local cortical topology. In this way it will be possible to determine whether the current lies perpendicular to the cortical surface or parallel. It would be the former if pyramidal cells or dendrites of other cells having preferred vertical orientations are responsible for the field, and the latter if directed projections from one area of cortex to another are responsible. Thus, important information concerning the underlying physiology can be deduced. Algorithms for digitizing the MRI scans and exploiting information provided by Halo have been developed by Ms. Gladys Klemic, a graduate student.

Profile: Software to Depict a Current Dipole in the Head

A graphics program christened "Profile" has been developed by Mr. Lian Tao, a graduate student, to relate the locations of deduced neural activity in the brain to external features of a subject's head. Profile displays on a terminal screen, or plots on an X-Y digital recorder, the three orthogonal profiles of a subject's head. The data are obtained by use of a 3D digitizer or the Probe Position Indicator system. The user chooses the side of the head to be displayed in the sagittal cross section, as well as whether the transverse cross section is to be depicted from below or above, and whether the coronal cross section is seen from in front or in back. On each cross-section is shown the position and orientation of the dipole (or dipoles) that are deduced from field measurements to account for a measured field pattern. A vector depicts the dipole, and its length denotes the current dipole moment. A rectangle centered on the position indicates the uncertainty in the location of the dipole. The sagittal profile can also be distorted slightly to insure that the subject cannot be identified.

Relationships Between Physiology and Perception

We have considered how the functional aspects of neural activity in auditory cortex revealed by magnetic studies may relate to human perception or performance. The possibility of establishing such relationships is based on earlier studies of activity in visual cortex, where research in our laboratory showed that simple reaction time varies with stimulus parameters in the same way as the neuromagnetic latency for observing maximum field strength. This correspondence was established for the latency of steady-state responses to contrast-reversing grating patterns, where latency was found to increase with (1) increasing spatial frequency (Williamson et al. 1978), (2) decreasing contrast (Okada et al. 1982b) and (3) decreasing luminance (Okada et al., unpublished). We investigated a different aspect of neural activity in auditory cortex, taking advantage of the fact that neuromagnetic theory shows how quantitative measures of neural activity may be determined, both in source strengths and source position in three-dimensional space. Our earlier studies of auditory responses combined with recent findings in other laboratories is a fertile basis for developing such relationships.

In 1982 studies by Romani et al. (1982a,b) demonstrated the existence of at least one tone map across human auditory cortex. The stimulus was a tone whose amplitude

was sine-wave modulated at nearly 100%, and the magnetic response at the modulation frequency was mapped over the temporal and parietal areas of the head. Measurements of the total strength of the equivalent current dipole accounting for the observed field pattern showed that source strength is independent of tone frequency for a given subject. Also, for two subjects studied, strength was also independent of subject. From the current dipole moment of the source, the minimum number of cells responding to a given tone was estimated to be some 10^4. Thus a sizeable population is responsible for the observed magnetic field. The spatial extent of such a population cannot be inferred from the data (Okada, 1985), but a population of 10^4 neurons could be highly localized since some 10^5 neurons are found under each square millimeter of cortical surface. It is unlikely that the population is so widely distributed as to be spread over an area with linear dimensions as great as a centimeter in each direction, for the entire tonotopic sequence extends over a track having a length on the order of 3 cm.

Recently, Pantew et al. (1988) reported neuromagnetic evidence for a tonotopic sequence for the N100m component of the transient response to a tone burst. The general locus of activity agrees quite well with the trend observed in the steady-state response, with responses to tones of higher frequency lying deeper beneath the scalp. Thus both the N100m and steady-state response (the latter having an apparent latency of about 50 ms) are tonotopically organized. There is evidence these maps do not coincide, for careful measurements by Pelizzone et al. (1984) for the magnetic field patterns of N100m and steady-state response evoked by 1 kHz tones show that the two sources lie at the same depth but the steady-state response lies 1 cm more posterior than the transient.

Hoke et al. (1988) have recently reported evidence for an amplitopic map for the N100m component, and the trajectory of this sequence across cortex is approximately at right angles to that of the tonotopic sequence, with activity shifting toward shallower depth and anteriorly with increasing stimulus intensity. Here as well as for the tonotopic sequence, there is a logarithmic representation, with cumulative distance across the cortex between one region of activity to another being proportional to the logarithm of the sound intensity. Each 10 dB increase in sound intensity produces a shift of about 0.3 cm across cortex.

The tonotopic and amplitopic functional maps have an interesting relationship to psychophysical studies of perception, and the two measures taken together provide an important physiological implication. To see this consider the fact that the just-noticeable tone difference for pitch discrimination at low levels of intensity is roughly proportional to frequency. This holds for frequencies down to about 1 kHz for studies with frequency-modulated tones (Shower and Biddulph, 1931) and down to about 500 Hz for successively presented tone bursts (Wier et al., 1977). These and other psychophysical data are discussed by Scharf and Buus (1986) in the *Handbook of Perception and Human Performance* (K.R. Boff, L. Kaufman, and J.P. Thomas, 1986). The just-noticeable tone difference at a frequency f for tone bursts corresponds to a frequency shift of about $1\times 10^{-3}f$. The tonotopic map reported by Romani et al. (1982b) indicates that a relative frequency shift of $\Delta f/f$ corresponds to displacement of activity across cortex by $\Delta D = 0.58(\Delta f/f)$ cm. Therefore the just-noticeable tone difference at low sound intensities represents a fixed shift of activity across cortex of about 6 μu. This is a remarkably short distance. It is much less than typical 'minicolumn' of Montcastle (1979), which is about 50 μ in diameter as determined by Nissl stain, and is even much less than the size of a single pyramidal cell, as gauged by the extent of dendritic arborization. Yet the

population of cells responding to the stimulus is on the order of 10^4 neurons.

It appears therefore that a perceptually different tone is not distinguished by a discrete shift of all activity from one region of cortex to another (perhaps adjacent) one, as would be the case were it to shift from, say, one minicolumn to another. Instead the distance by which activity shifts is much smaller than the linear extent of the responding population. If tone discrimination is associated with activity giving rise to either the P50m or N100m transient components, the process may well depend on small shift in the position of the maximum of activity that is distributed along the cortex. It seems is unlikely that the physiological processes underlying pitch discrimination are to be found at subcortical auditory nuclei, where tonotopic maps are also found, because these maps show more convergence (shorter total length of the tonotopic sequence) than at cochlea or cortex (Clopton et al. 1974).

The fact that very small displacements of activity across cortex may correspond to perceptual differences has been revealed previously in electrophysiological studies of activity in auditory cortex of the mustached bat, *Pteronotus parnellii parnellii*. Suga and Horikawa (1986) found that the just-noticeable range difference for determining the distance of a target at mid-range is about 1.3 cm, and this corresponds to a shift across cortex of about 6 μ . Thus, fine-grain sensitivity is found for a variety of function sequences, in both primates and non-primates.

We may also consider psychophysical implications of the other dimension across auditory cortex - the amplitopic map. Our analysis of the data of Pantew et al. (1988) indicates that there is a shift of approximately 0.3 cm across cortex for each 10 dB increase in sound intensity. For a small relative change $\Delta I/I$ of intensity the corresponding displacement would be: $\Delta D = 0.13\ \Delta I/I$ cm. The data of Rabinowitz et al. (1976) and Jesteadt, Wier, and Green (1977) for just-noticeable differences in intensity show that discrimination improves with increasing intensity, from $\Delta I/I = 12 \times 10^{-2}$ at a sensation level of 40 dB to 5×10^{-2} at a sensation level of 80 dB. Accepting for the sake of illustration an intermediate value of 7×10^{-2} leads to the conclusion that the just-noticeable difference in sound level corresponds to a displacement of activity across cortex of about 100 μ .. This is considerably greater than the minimum displacement along the tonotopic sequence corresponding to the just-noticeable tone difference. We may infer that if such discrimination is carried out by regions of cortex monitored magnetically, the neural circuits responsible for amplitude discrimination differ from those for tone differences. Indeed, the minimum required shift along the amplitopic sequence to account for the just-noticeable loudness difference is sufficiently large as to admit the notion that activity is displaced from one set of minicolumns to another. Since an area of cortex of 0.1 mm^2 is sufficient to account for activity of 10^4, it is not inconceivable that the active region for a given intensity is 100 μ along the amplitopic sequence and 1,000 μu at right angles to it. There is, however, no direct evidence that the active area is indeed so small or that it extends only 100 μ along the sequence. These considerations have been submitted for publication as part of a book chapter (Williamson and Kaufman 1988).

Method for Locating a Small Magnetic Object

During the course of this program we were presented with an opportunity to investigate the feasibility of using SQUID systems to locate a small magnetic object within the human body. While such an object would be modeled as a magnetic dipole, not a current dipole, we concluded that similar techniques could be applied in mapping the field pattern and using them to deduce where the object lies. Success in using such a procedure for a magnetic dipole would give additional confidence for using analogous procedures of localization for current dipoles. Furthermore, having a technology for detecting objects too small to be imaged by x-rays may have a variety of important applications.

The object of interest was a piece of a thin acupuncture needle lodged under the right scapula of a young male adult. It was estimated to be about 5 mm in length and only 0.2 mm in diameter. The needle could not be found in surgical procedures accompanied by studies of 30 standard X-ray images. To locate it, we mapped the magnetic field component normal to a plane lying above the object, using a standard SQUID neuromagnetometer. Assuming that the needle could be modelled as a magnetic dipole, we were able to infer its lateral position, depth, orientation, and magnetic moment. With this information, directed CT scans, high-resolution X-ray films, and the subsequent surgical removal of the needle proved that it could be located in the body with an accuracy of better than three millimeters. The principle limit on this accuracy is in specifying the location of the object relative to reference positions on the overlying skin. In this instance, different placements of the patient's right arm caused the skin to be displaced relative to the rib cage. Therefore, to achieve accurate localization the patient had to assume a given position for both the neuromagnetic studies and surgical procedure. This work was done in collaboration with Risto J. Ilmoniemi, Ph.D., Harold Weinberg, M.D., and Arthur D. Boyd, M.D.

To map the magnetic field pattern over the back, our patient lay prone on a firm bed, which was supported by rollers. During a scan, the bed was smoothly moved under the magnetometer, while its position was monitored by the voltage from a linear potentiometer attached to the bed. Each linear scan was performed three or more times to assure reliability; upon completion of a set of scans, the bed was displaced laterally by 2 cm and another set of scans was recorded. A pointer mounted on the dewar holder enabled us to reference positions across the plane of measurement to positions on the posterior torso. The only significant source of noise was a slow variation of the ambient field, which produces a drift of the baseline. The first depended upon identifying the positions of the positive and negative field extrema, as well as determining the values of the field at these extrema. We developed a procedure whereby this information is sufficient to determine the three position coordinates of the dipole, the two angles specifying its orientation, and the moment specifying its strength. We developed a set of curves that enables these parameters to be determined without recourse to a computer. A second method was based on using a computer routine to determine the least-squares fit to the field pattern. The deduced positions of the dipole determined by the two methods agreed to better than 3 mm, with the least-squares method being the more accurate because it more effectively averages over imprecisions in the data.

Several verification tests were carried out with a 15-mm length of an acupuncture needle mounted on the subject bed, so that its position and orientation could be directly measured, confirmed the accuracy of this analysis. In fact, it was found that instrumental

noise caused an error of only 0.8 mm in position. The position indicated by the magnetic analysis was used to determine where CT scans should be made, in an attempt to confirm the presence of the needle. Transverse scans through the thorax were obtained through the predicted location at 3-mm displacements longitudinally. A small (1-2 picture elements) high-density feature was evident in a single scan within the intercostal space between the fifth and sixth ribs, at the predicted depth and lateral position. Based on this information, a surgical procedure was scheduled. On the morning of the procedure, magnetic scanning was repeated with the subject prone and right arm raised above the head, mimicing the position to be assumed during surgery so that the deduced position could most accurately be related to marks placed on the skin. Subsequently, a high-resolution X-ray film was obtained for a frontal cross section of the upper right thorax, and it showed the needle curved at the lateral position indicated by the magnetic analysis. CT scans taken through and near the magnetically deduced position again confirmed the presence of the needle at the predicted depth. A surgical procedure was conducted with the incision made directly above the position indicated by the magnetic and X-ray studies. As soon as the depth of the incision was about 25 mm, the needle was observed in a curved configuration within the intercostal space between the fifth and sixth ribs, and it was removed. A manuscript describing this study has been accepted for publication in the IEEE Transactions of Biomedical Engineering (Ilmoniemi et al. 1987).

A New Method for Calibrating Multisensor SQUID Systems

Increasing interest in determining the strength of neural sources as well as their positions in the shortest possible time has drawn attention to the need for fixed arrays of sensors and for a method to accurately calibrate the individual sensors. Very accurate calibration is not of prime interest when an array is moved from one place to another sequentially to determine a field pattern, because generally the array is rotated from one measurement to the next in a quasi-random manner so that the effect of calibration inaccuracies tends to average toward zero. However, high accuracy becomes important when the array monitors the field pattern at a set of fixed positions over the scalp. We have developed a technique with a relative accuracy of about 2% for calibrating individual sensors in a neuromagnetic probe, whose detection coils have the popular geometry of a second-order gradiometer. This procedure was described in a manuscript that will appear in the July 1988 issue of IEEE Transactions of Biomedical Engineering (Costa Ribeiro et al. 1988).

It is quite simple to place a small calibration coil under the dewar, feed an ac current through its windings, and move the coil so that the sensor's output is maximized, thereby indicating the coil is centered on the axis of a given detection coil. However, the magnitude of the sensor's output is very sensitive to the distance between the calibration coil and detection coil, and this distance in general is not known to within the required fraction of a millimeter to achieve 1% accuracy. In practice the result has an accuracy of perhaps only 10%. A variation of this procedure relies on placing the coil in succession at a number of precisely determined locations sufficiently far from the probe that the field of the coil at the sensors is accurately dipolar. From the recorded outputs of all sensors for each coil location, high accuracy may be obtained when the calibration factors are determined by a least-squares fit (Ilmoniemi et al. 1988).

We have successfully applied another method for calibrating second-order gradiometers that relies precisely on the fact that such coils are relatively insensitive to a uniform field. The procedure is to use a large, square field coil whose sides (2.64 m length) are roughly two orders of magnitude greater than the baseline of the detection coil. A large *calibration coil* is placed so that the detection An ac current at 20 Hz is provided by a function generator, and the corresponding output of the SQUID electronics was amplified, bandpass filtered, and monitored by a digital voltmeter. This output is proportional to the difference between the field at the center coil and end coil of the detection coil, a number that is easily calculable from the known dimensions of the calibration coil and detection coil. Of particular importance is the fact that the net flux in the detection coil is insensitive to its exact position with respect to the calibration coil: moving one upward or downward by 4 cm produces only a 1% change in the value of the calibration factor. This is the desired feature of the large-coil technique.

The calibration factor determined in this way is accurate only to the extent that the detection coil's field balance (match of the area-turns ratio of all the coils of the gradiometer) is sufficiently high. The field imbalance can be determined by applying a uniform field and measuring the resulting output voltage of the sensor. For this purpose, a reasonably uniform field can be produced with a set of four coaxial, square coils of side 2.64 m (Merritt et al. 1983). The number of turns of wire in the four coils was originally 59,25,25,59. These field coils were positioned with an accuracy of better than 2 mm in an attempt to achieve sufficient field uniformity. Precise measurements of the resulting axial field profile (in the vertical direction) were made by differential methods with a fluxgate magnetometer to verify the quality of uniformity. They showed that the steel reinforcing rods in the concrete floor of the laboratory enhanced the field produced by the lowest coil and shifted the field center upwards from the geometrical center of the coil set. This effect could be countered by removing two turns of wire from the lowest coil.

To measure the effect of field imbalance in the windings of the detection coil, a 20-Hz current was passed through the uniform-field coil, and the corresponding ac output voltage of each SQUID system was noted with a digital voltmeter. Correcting for the small (about 3.5%) nonuniformity of the field yielded the field imbalance factor for each detection coil, which was on the order of 10^{-5}. Taking this into account for the measurements with the calibration coil yielded the calibration factor for the sensor. This is typically about 1.2×10^{-7} tesla/volt for the sensors in our 5-sensor probe (Freddy). The value of the calibration factor for each coil could be determined reproducibly with an accuracy of 2%. In comparing calibration factors across coils we found a 10% spread in their values, which may be attributed to differences in the construction of the SQUID systems.

A Method of Verification

Another way to measure the field imbalance correction, which at the same time verifies the value for the field calibration factor, is to measure the change in the output when the calibration coil is moved axially up or down by a known distance. If the displacement is small it is enough to consider the field profile only up to the fourth-order term. When displacing the calibration coil in our system by 4 cm the output voltage changes by only 1%, in agreement with the theory.

Single-Position Calibration

Another advantage of using a single large external coil for calibration is the possibility of doing it rapidly for all the sensors in an array. In fact it is not necessary to place each detection coil at the center and coaxially aligned with the calibration coil. The field produced by a large square calibration coil can be computed for the position of each turn of each detection coil. The theory for this was developed. Although this calibration procedure is comparatively insensitive to the vertical position of the calibration coil, it is nevertheless sensitive to other parameters such as the size of that coil: a 1% change in the length of the sides of the calibration coil affects the calibration by 3%. On the other hand, an error in the angular orientation by 1 deg affects the calibration by only 0.16%. Another advantage of this single-position calibration, beyond its rapidity, is the possibility of using it to determine the exact angular position of the array relative to a fixed laboratory frame of reference (the calibration coil) during an experiment where the array is tipped in order to be positioned over the source. The calibration factors can be determined prior to such a measurement, with the array upright, by passing a known current through the calibration coil.

Sources of Error in Determining the Location of a Neural Source

The early success of neuromagnetism motivated the development of magnetic sensing systems to measure the magnetic field near the scalp at several positions simultaneously. Probes with 4, 5, and 7 sensors are presently in use (Ilmoniemi 1984; Williamson et al. 1984; Romani 1985). In addition to greatly reducing the time required to record a field pattern, these multi-sensor systems make it possible to determine the position, strength, and orientation of a localized neural current source with a *single-position measurement*, that is, without having to move the probe from one place to another. A particular advantage of this is the possibility of following subtle shifts of activity between adjacent neural populations in studies such as those recording responses evoked by visual patterns of differing content.

The effects of calibration error and magnetic noise on the accuracy of locating an equivalent current dipole source in the human brain were investigated by computer analysis for 5- and 7-sensor probes and for a pair of 7-sensor probes. The importance of using a large array, with sensors strategically placed, is illustrated by an analysis for case when the probe is placed at a field extremum. Then a noise level of 5% of peak detected signal produced uncertainties of about 20% in source strength and depth for a 5-sensor probe. These are reduced to 8% when the array is increased to a pair of 7-sensor probes, and uncertainties of about 15 mm in lateral position with the 5-sensor probe are reduced to 1 mm for the pair of 7-sensor probes.

The head was modeled as a uniform sphere or a set of concentric spherical shells of differing conductivity, representing regions such as the brain, skull, and dermis. The source was modeled as a current dipole, which is described by five parameters: its position (x, y, z), orientation ψ of its moment in the plane tangential to the radius passing through its location, and the value Q of this moment. The five field values obtained from a single-position measurement with a 5-sensor probe are sufficient to determine these five parameters, provided that the probe is not centered on certain symmetry lines or

points, such as directly over the dipole (Hämäläinen et al. 1985; Ilmoniemi 1985). Indeed, if additional information is available to fix the orientation of the source, a four-sensor system may serve for locating a dipole (Vvedensky et al. 1988). However, we might expect that locating a dipole with a 4- or 5-sensor system is very sensitive to calibration errors since the parameters are not overdetermined by the data. The computations were made for successively larger arrays of sensors presently in use: a 5-sensor probe with 4 outer coils equally spaced about a central coil; a 7-sensor probe with 6 outer coils equally spaced about a central coil; and a pair of 7-sensor probes (hereafter called a 14-sensor system). The probe in these computations was placed directly over a position on the scalp where the normal component of the field is maximum, which is useful for achieving good accuracy in determining the depth and strength of a current dipole. The five-sensor probe we considered has a set of five detection coils (Freddy), each being a second-order gradiometer with a coil radius a = 0.75 cm and baseline b = 4.0 cm between adjacent coils. The coils are arranged in the pattern of a cross, so that the centers of the pickup coils (lowest coil of the gradiometer) of the four outer coils are 2.0 cm from the axis of symmetry. The seven-sensor probe is identical to the 5-sensor probe except that it has two additional outer sensors, thus forming a hexagonal array about the center coil. The fourteen-sensor probe consists of two 7-sensor probes, positioned at each field extremum with identical orientations.

Effect of Calibration Errors

Certain detection coil positions play more important roles than others in determining the values of various dipole parameters obtained from a least-squares fit to the data. To illustrate this we computed the consequence of a calibration error in any one of the sensors. Nonlinearity in the relationship between field values and best-fitting parameters was evident, because identical positive and negative increments generally changed each parameter in opposite directions but by different amounts. We took the larger change to characterize the corresponding uncertainty in the best-fitting value. Our computations show that an error as small as 1% in *any* sensor causes the dipole to rotate and shift by ~5 mm in the coordinate z longitudinal to the direction of the dipole. If the errant sensor lies off the axis passing through the extrema of the field pattern, the shift is due to breaking of mirror symmetry about this line.

The lateral position x is influenced most strongly by errors in the center sensor and the one farthest from the dipole. The center field in comparison with fields at the outer sensors fixes the depth of the dipole and therefore how far it lies from the probe. Longitudainal position z is also influenced more strongly by coils lying farther from the dipole. The orientation ψ of the dipole's moment is related to this, being most sensitive to error in the farthest sensor, with all of the others being much less important. The deduced depth d of the dipole is most sensitive to a calibration error for the center sensor. This is because its signal in comparison with those of the outer sensors determines the scale length of the pattern: a stronger signal decreases the length scale, thus implying a shallower dipole, and *vice versa*. The strength Q of the dipole is also most sensitive to the field indicated by the center sensor. While Q is directly related to the field at the extremum it is also affected by the depth of the dipole: to produce a given maximum field, the deduced Q must increase with increasing depth.

Similar computations have been carried out for 7-sensor and 14-sensor probes. The effects of calibration errors for the center sensor, sensors nearest the dipole, or sensors farthest from the dipole are similar, but the magnitude of the maximum shift of a dipole parameter is generally reduced. Part of this advantage comes from the effect of diluting the importance of any one sensor when the total number of sensors is increased, and in the case of the 14-sensor probe part comes the broader expanse of the field pattern that is sampled. One exception to the improvement in accuracy with increasing number of sensors is determination of the parameters Q and d with the 5-sensor and 7-sensor probes. This is because the center sensor has dominant importance for these parameters in comparison with any of the outer sensors, so a calibration error for the center sensor produces virtually the same change in Q and d for both the 5-sensor and 7-sensor probes. To emphasize this point, there is a dramatic improvement in the precision for Q and d when the second 7-sensor probe is positioned over the other field extremum to produce a 14-sensor system. Determining the locations of the two extrema fixes the length scale of the pattern more firmly than the ratio of central to outer fields of any one extrema, thus reducing the importance of both center sensors.

From these trends we conclude that the scalar properties (strength Q and depth d) have values that are most sensitive to calibration errors in the central sensor, whereas the vector properties (longitudinal and transverse position, as well as orientation) are most sensitive to the coils placed farthest from the source. We emphasize that these trends apply when the probes are placed directly over the field extrema, so as to monitor the strongest fields. There is no implication in this choice of position that it is optimal for determining the full set of dipole parameters; indeed, the optimal position and orientation of the probe will depend on the parameter of interest and on the depth of the dipole.

Influence of Noise on Locating a Source

The preceding discussion of calibration errors has a straightforward extension to the effect of field noise on the uncertainty in the best-fitting values of the dipole parameters. For simplicity we assume that the noise in the various sensors is uncorrelated and of the same rms value. To generalize the discussion, it is convenient to express the rms field noise in any sensor in terms of the field at the positive extremum. Thus, when the same normalized noise amplitude is applied to an outer coil, which has a lower signal level, the actual signal-to-noise ratio for that coil is worse than for the center coil. The results for the 5-sensor, 7-sensor, and 14-sensor probes are shown in Table I. On going from 5 to 7 sensors, there is substantial improvement in reducing the uncertainties for some parameters (x, z, ψ), while there is very little benefit for others (Q and d). The most dramatic improvement is obtained on going from the 7-sensor to 14-sensor probe, where all the uncertainties are diminished. The reason is evident: On going from 5 to 7 sensors the additional outer detection coils enhance the probe's ability to resolve asymmetry in the field pattern, and this better establishes the position (x,z) and orientation ψ of the source with respect to a field extremum. A similar improvement is seen on going from 7 sensors to 14 sensors, but there is also a marked improvement in determining Q and d. The latter benefit was gained because placing a second probe over the second field extremum accurately fixes the distance between the extrema of the pattern, thereby more accurately determining d. Then the average of the field values accurately fixes Q. In addition, determining the general location of both extrema limits the uncertainty in the dipole's

TABLE I

Magnitude of the uncertainties in best-fitting current-dipole parameters for various levels of field noise in the sensors. Noise is expressed as a percentage of the dipole's field at a field extremum. The dipole is located at a depth of 2 cm beneath the surface of a uniform conducting sphere of radius 9 cm.

PROBE (%)	NOISE (%)	$\delta Q/Q$ (%)	$\delta d/d$ (%)	δx (mm)	δz (mm)	$\delta\psi$ (deg)
5-sensor	5	21	16	4.6	13.6	40
	10	42	31	6.7	20.0	64
7-sensor	5	20	15	1.2	4.0	12
	10	44	31	2.6	8.1	14
14-sensor	5	8	6	0.4	1.0	3
	10	16	11	0.8	1.9	6

orientation ψ. This was said in a different way by Ahonen et al. (1986) who noted that the accuracy of a dipole fit is enhanced for an array of sensors if the lateral spacing between their detection coils is increased, even if the dipole lies at a relatively shallow depth. Cuffin (1986) has also considered the effect of noise on dipole localization for several types of measurements, and although the position of the probe in his calculations does not coincide with ours there is general agreement between his results and ours for the uncertainty in strength, orientation, and depth of the dipole source.

It may be concluded that the 5-sensor probe with a 10% noise level produces rather poor results: the source strength is known to only about 40%, its orientation to only 60°, and the lateral position to only 2 cm. Decreasing the noise to 5% provides substantial improvements, with uncertainties that are comparable to much of the data being reported in the literature with a single sensor being used for sequential measurements at some 30 or more positions.

The main advantage in adding two more sensors to produce a 7-sensor probe is in improving the uncertainty in position and orientation of the dipole. For a comparable noise level, these uncertainties are reduced by a factor of 2 - 3. A further reduction of ~3

is achieved in the uncertainties for *all* parameters by going to a 14-sensor probe. Here the results are comparable to what might be considered state-of-the-art, where Q and d are known to about 10%, transverse position to 1-2 mm, and orientation to 10°. Clearly, a 5% noise level with a 14-sensor probe would represent a substantial advance on this. High precision of this type is advantageous when searching for subtle changes in position or orientation of a confined neural population under study. These small uncertainties are comparable to the practical limits imposed by variability of many types of biomagnetic activity and by errors attendant to positioning a probe over the scalp.

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